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Anxiety and Risk of Incident Coronary Heart Disease: A Meta-analysis.

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Abstract

Objectives: Our objective was to assess the association between anxiety and risk of coronary heart disease (CHD).

Background: In contrast to other negative emotions, such as depression, less research has focused on the association of anxiety with incident CHD.

Methods: A meta-analysis of references derived from MEDLINE, EMBASE and PSYCINFO (1980- May 2009) was performed without language restrictions.

Endpoints were cardiac death, myocardial infarction (MI) and cardiac events. The authors selected prospective studies of (non-psychiatric) cohorts of initially healthy persons in which anxiety was assessed at baseline.

Results: Twenty studies reporting on incident CHD enclosed 249.846 persons with a mean follow-up period of 11.2 years. Anxious persons were at risk of CHD (hazard ratio (HR) random: 1.26; 95% confidence interval (CI): 1.15-1.38; $p<0.0001$) and cardiac death (HR: 1.48; 95% CI: 1.14-1.92; $p=0.003$), independent of demographic variables, biological risk factors and health behaviors. There was a nonsignificant trend for an association between anxiety and non-fatal MI (HR: 1.43; 95% CI: 0.85-2.40; $p=0.180$). Subgroup analyses did not show any significant differences regarding study characteristics, with significant associations for different types of anxiety, short and long-term follow-up and both men and women.

Conclusions: Anxiety appeared to be an independent risk factor for incident CHD and cardiac mortality. Future research should examine the association between anxiety and CHD with valid and reliable anxiety measures and focus on the mechanisms through which anxiety may affect CHD.

Abbreviation list

CHD= Coronary Heart Disease; MI= Myocardial Infarction; CI= Confidence Interval;

HR= Hazard Ratio.

Introduction

Research has demonstrated an association between psychological factors such as stress, and both the development of coronary heart disease (CHD) and CHD outcomes [1,2]. Most studies have focused on the role of depression, with several meta-analyses indicating that depression is an independent risk factor for the development of CHD in the general population [3], as well as a prognostic risk factor in CHD patients [4].

While evidence suggests that anxiety also has an adverse impact on prognosis in CHD patients independent of depression [5-8], the role of anxiety as an etiological risk factor is less clear. While several studies suggest that anxiety may contribute to the development of CHD in initially healthy individuals [9] and found an effect on cardiac death [10-12] or incident myocardial infarction (MI) [13,14], others have found no association [15,16].

Meta-analytic research may help to resolve these inconsistencies but, to our knowledge, no recent meta-analysis has yet been conducted on the association between anxiety and incident heart disease. The present meta-analysis therefore focuses on the impact of anxiety on the development of CHD in initially healthy persons. The first objective of this study was to investigate the association of anxiety with incident CHD independent of traditional cardiovascular risk factors. The second objective was to examine whether the associations between anxiety and incident CHD were different for MI versus cardiac mortality as outcomes.

Methods

The aim was to assess the association between a comprehensive set of common anxiety constructs (including anxiety, panic, phobia, post-traumatic stress, and worry) and incident CHD. We identified all studies available by May 2009, on the

development of CHD in anxious versus non-anxious persons. Methods for systematic identification, appraisal, synthesis and statistical aggregation of information, and reporting of results were chosen according to predetermined methods [17,18].

Literature search

The electronic databases MEDLINE, EMBASE and PSYCINFO (1980- May 2009) were searched using the following terms: “(community or cohort or healthy persons or risk) and (anxiety or post traumatic stress disorder or tension or anxiety symptoms or anxiety disorder or panic or panic attacks or phobic anxiety or phobia or worry) and (mortality or coronary mortality or myocardial infarction or coronary heart disease or sudden cardiac death)”. There were no language restrictions and both published and unpublished data were included. In addition, reference lists of included studies and review articles were checked to identify additional studies meeting selection criteria.

Selection

Two independent raters (A.R. and J.D.) identified studies meeting the following pre specified inclusion criteria:

1. Studies were prospective in nature, following a (non-psychiatric) cohort of initially healthy persons over time.
2. At baseline, studies had to include at least one self-report or interview-based assessment of anxiety symptoms or anxiety disorder; e.g., post traumatic stress disorder, tension, worry, phobic anxiety, panic, or generalized anxiety disorder.
3. Endpoints included cardiac mortality or MI.

Studies focusing explicitly on older persons (over 75 years old) were excluded.

During the selection procedure, in case of disagreement between the two raters, the four investigators discussed the difference of opinion until consensus was reached. When study samples included healthy persons combined with a small number of heart disease patients, these studies were included when the original study adjusted for the presence of medical conditions [15,16,19-22]. Regarding multiple reports on the same dataset, only one paper was included based on the anxiety measure, study sample, endpoint, and follow-up period, preferring (in order of importance) general anxiety measured with a reliable and valid measure, multiple cardiac endpoints (e.g., cardiac mortality and MI), larger sample sizes, and longer follow-up periods. Regarding the different papers reporting on the Normative Aging Study, the study of Kubzansky et al. [23] was included because this study reported on general anxiety as measured with the Minnesota Multiphasic Personality Inventory (MMPI) and on non-fatal MI and cardiac mortality. We included both studies of Haines et al. [10,24], as they represented different outcomes. We retrieved the association between phobic anxiety and cardiac mortality from the later study (given the longer follow-up period) [24], and the association between phobic anxiety and MI from the earlier study [10]. If necessary, the corresponding authors of the eligible studies were asked to provide additional information.

Information on sample size and characteristics (e.g. did the researchers include specific in-/exclusion criteria such as gender), anxiety assessment, endpoints, participation rate, percentage lost to follow-up, follow-up duration, bivariate and fully-adjusted relative risks and 95% confidence intervals (CI), and variables used in multivariable analysis was abstracted and evaluated. We did not weigh the contribution of each study to the meta-analysis on the basis of quality scoring for

there are no validated measures of quality for observational studies and the use of subjective rating scales may lead to bias [25].

Endpoints

We examined the association between anxiety and incident CHD. If a study reported on MI and cardiac mortality separately, we included cardiac mortality as endpoint [23,26]. Concerning the papers of Haines et al., we included their study reporting on cardiac mortality [24]. We focused on hard medical endpoints and, if possible, kept angina out of our analysis [23,27] because anxiety may be associated with the report of symptoms of chest pain without reflecting underlying CHD [27]. One included study reported on a broader endpoint, namely cardiovascular events (including cardiac death and non-fatal MI) [19]. We also examined the associations between anxiety and non-fatal MI and cardiac mortality (including sudden cardiac death and other cardiac death) separately.

Quantitative data synthesis

Data from all studies were pooled. We combined hazard ratios, relative risks and odds ratios from multivariable analyses. For one paper we had to recalculate the CI [22] because the log values for lower and upper limits were not symmetric. We suspected a relatively large heterogeneity in results given that the included studies differed in anxiety types, anxiety measures, and sample characteristics (e.g., gender). We therefore used the Random Effects Method to generate a summary estimate of effect estimates and tested the amount of heterogeneity with the Q test of homogeneity and the I^2 test, which indicates the proportion of total variance explained by heterogeneity. In one study the relative risk of anxiety predicting CHD was expressed relative to a standard deviation increase in anxiety score [28]. We calculated a new relative risk

and CI, based on the assumption of normal distribution, assuming that 20% of the sample experienced increased anxiety (mean anxiety prevalence of other included studies).

If a study included various scales of the Crown Crisp index, e.g. Haines et al. [10,24], the phobic anxiety scale was selected because it was most representative of other studies using the Crown Crisp Index [11,26]. If the association between anxiety and CHD was assessed separately for men and women, we included that study twice with sample sizes according to the number of men and women in the study [22,28]. In the studies from Eaker et al. [28,29], the tension scale was used because it reflects psychological symptoms of anxiety whereas the anxiety scale mainly reflects physiological arousal [28] that may be confounded by underlying cardiac disease. We conducted a subgroup comparison between studies including all persons versus studies focusing on the contrast between high versus low anxiety subgroups.

If study outcomes were heterogeneous based on the I^2 test/Q test, the possible effects of anxiety type, follow-up period and study sample (healthy persons versus healthy and heart disease patients and men versus women) were studied.

Differences in effect estimates between the subgroups were assessed by comparing the pooled effect estimates using chi-squared analysis, comparing logarithms of these estimates. In order to evaluate the presence of publication bias, a funnel plot was constructed by plotting the effect measure against the inverse of its standard error. We used Egger's test of the intercept, the classic fail-safe N and Duval and Tweedie's Trim and Fill test to estimate the severity of publication bias. All analyses were performed with the program Comprehensive Meta-Analysis version 2.

Additional information by personal communication

The author of one included study was contacted for further information and supplied us with the multivariable hazard ratio (HR) of anxiety predicting cardiovascular events [19].

Results

A flow diagram of the literature search is shown in Figure 1. The agreement rates (Cohen's kappa) for the 2 steps in the selection procedure were 0.81 and 0.94 respectively, indicating very good consistency of judgment by raters [30]. Twenty-one studies, published between 1987 and 2009, met selection criteria of which the characteristics are shown in tables 1 and 2. Of these studies, 20 reported on incident CHD, 9 on cardiac mortality and 5 on non-fatal MI.

Incident CHD

Twenty studies that reported on incident CHD enclosed 249,846 persons. Mean follow-up period was 11.2 years, with follow-up periods ranging from 2.0 to 20.9 years. The mean age at baseline assessment ranged from 38 to 72 years. Eleven analyses reported on males, 7 on females and 4 on a combined sample of males and females. Fourteen analyses (70%) showed a statistically significant univariable association between anxiety and CHD and 10 (50%) were significant in multivariable analyses (table 2).

The pooled HR for incident CHD (favoring cardiac death in case of multiple endpoints) was 1.26 (95% CI: 1.15-1.38; $p < 0.0001$) when pooling multivariable and bivariate HRs, in case no multivariable HR was reported in the original study [27,33] (Figure 2).

Cardiac mortality and MI

Nine of the 21 included studies focused on cardiac mortality as a separate endpoint. Five studies found a significant association between anxiety and cardiac mortality [11,21,26,34,35], of which 3 remained significant in multivariable analyses [11,34,35]. The pooled multivariable HR for cardiac mortality was 1.48 (95% CI: 1.14-1.92; $p=0.003$). The heterogeneity was lower than for incident CHD ($Q=17.61$; $p=0.024$; $I^2=54.57$).

Five studies focused on non-fatal MI as a separate endpoint. Two studies found a significant association between general anxiety and MI [23,33], although one did not adjust for confounders [33]. The pooled HR for non-fatal MI was 1.43 (95% CI: 0.85-2.40; $p=0.180$). When excluding the paper that did not adjust for confounders [33], the HR decreased to 1.23 (95% CI: 0.74-2.05; $p=0.416$). There was no significant difference between the impact of anxiety on cardiac death versus non-fatal MI ($p=0.91$).

Subgroup analyses

Studies which included all persons in their analyses had a smaller pooled HR (1.19; 95% CI: 1.07-1.33) in comparison with studies focusing on the contrast between high versus low anxiety subgroups (HR: 1.39; 95% CI: 1.16-1.66), but this difference was not statistically significant ($p=0.15$). There were no further differences for study sample, anxiety type and follow-up period.

A funnel plot of selected studies on the primary outcome suggested the presence of publication bias. Egger's test showed a significant asymmetry ($p<0.0001$). The Fail-Safe N shows that another 389 null-studies are needed in order for the p -value to exceed 0.05. According to the Trim and Fill test, the association between

anxiety and CHD remains significant after imputing possible missing studies (HR: 1.16; 95% CI: 1.06-1.28) (Figure 3).

Discussion

This is the first meta-analysis focusing on the association of anxiety with the incidence of CHD in initially healthy individuals. The results show an association between anxiety and incident CHD with a 26% increase in risk. Anxiety was also specifically associated with cardiac mortality, with anxious persons having a 48% increased risk of cardiac death. There was a trend for an association between anxiety and incident non-fatal MI, but this association was based on only 5 studies. Subgroup analyses did not show any significant differences regarding study characteristics with significant associations for different types of anxiety, short and long-term follow-up and both men and women. Secondary analyses in the original studies, excluding heart disease patients at baseline, did also not affect the results [19,20].

Recently published studies using large databases demonstrated a significant association between anxiety and MI [36] and panic disorder and CHD [37,38].

Strength of this meta-analysis is the adjustment for covariates in most of the individual studies that were included. Only 2 studies did not adjust for covariates [27,33], of which one reported a significant association between anxiety and MI [33]. All other studies adjusted for a variety of demographic variables, biological risk factors and health behaviors. After adjustment for these variables, the HRs decreased, but still remained significant.

It is important to compare the strength of the association between anxiety and incident CHD with other psychological constructs. A recent meta-analysis showed that depression was associated with a 46% increased risk of cardiovascular disease

[39], and the impact of depression on cardiac death (55% increased risk) was comparable to the impact of anxiety found in the present meta-analysis. Five studies on anxiety and CHD adjusted for depression in their analyses [20,23,34,40,41], and four associations remained significant [20,23,34,40]. In a study of Philips et al., subjects with both generalized anxiety disorder and major depressive disorder were at greatest risk of subsequent cardiac death, suggesting that anxiety and depression may also interact synergistically to affect CHD [21]. Anxiety and depression have a moderate to strong correlation and it is possible that anxiety and depression are both part of a larger and more stable psychological factor influencing heart disease, like negative affectivity [42,43]. A recent meta-analysis focusing on the association of anger and hostility with CHD found a 19% increased risk, but (a) this association was no longer significant after adjusting for possible behavioral covariates [44] and (b) the association with CHD mortality was not significant [44]. This difference in anxiety and anger as potential predictors of cardiac death is of interest, and calls for confirmation in future research.

There are several potential mechanisms that may help to explain the adverse association between anxiety and CHD. Anxiety has been associated with progression of atherosclerosis [45], decreased heart rate variability [46] and risk of ventricular arrhythmias [47,48]. Research supports the risk of arrhythmias particularly in the case of phobic anxiety, with studies showing an association between phobic anxiety and sudden cardiac death, but not with non-fatal MI [11,26]. More research is needed focusing on these possible mechanisms and the impact on different outcomes, particularly MI versus (sudden) cardiac death. Furthermore, anxiety is related to an unhealthy lifestyle in patients at risk of CHD [49]. In the present meta-analysis, unhealthy lifestyles (e.g. physical inactivity, increased body mass index and smoking)

were included as covariates, but they may also mediate the relationship between anxiety and CHD. This might indicate that the association between anxiety and CHD might be larger than reported here.

Anxiety can be treated effectively with cognitive behavior therapy and medications, e.g. benzodiazepines and selective serotonin reuptake inhibitors [50]. Unfortunately, many patients do not receive adequate treatment [50]. Besides the impact of anxiety on disability and decreased quality of life, clinicians should be aware of the risk of anxiety associated with incident heart disease. Future research needs to investigate whether the treatment of anxiety has a significant beneficial effect on the incidence or course of cardiac disease [51].

The results need to be considered in light of the study limitations. One important limitation in conducting a meta-analysis is the inevitability of combining data from studies that are not equally designed. Study samples were heterogeneous regarding age and gender and follow-up duration differed substantially across studies. Further, different anxiety measures were included, some of which were not extensively validated. As a result, the heterogeneity in our results is substantial. Also, only one included paper focused on an anxiety disorder, namely generalized anxiety disorder [21]. It is important that studies use a valid and reliable anxiety measure and more research is needed to the association of anxiety disorders with heart disease development. However, the finding of an association between anxiety and CHD was quite consistent across studies. Also, studies reporting on the Normative Aging Study showed comparable results for different anxiety types, such as post traumatic stress disorder [52] and worry [13], suggesting that a broad variety of anxiety symptoms influence incidence of CHD. Future research should focus on the specific aspects of anxiety that contribute to cardiac outcomes. Further, almost all studies were

conducted in Western populations which might limit the generalization of the findings. Another limitation concerns the proneness of meta-analyses to publication bias. We found an indication for publication bias, suggesting that the association between anxiety and CHD might be smaller than reported here. However, after adjusting for this possible bias the results still show a reliable association of anxiety with CHD.

In summary, anxiety was found to be an independent risk factor for the incidence of CHD and cardiac mortality in initially healthy individuals. The strength of this association appeared to be somewhat lower compared to the effect of depression but clearly higher than that of anger. Future research should examine the relationship between anxiety and CHD with valid and reliable anxiety measures, and needs to focus on the mechanisms through which anxiety may affect the development and onset of CHD.

References

1. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet* 2007; 370:1089-100.
2. Rosengren A, Hawken S, Ounpuu S, et al; INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364:953-62.
3. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003; 65:201-10.
4. Van Melle JP, De Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosom Med* 2004; 66:814-22.
5. Rothenbacher D, Hahmann H, Wüst B, Koenig W, Brenner H. Symptoms of anxiety and depression in patients with stable coronary heart disease: prognostic value and consideration of pathogenetic links. *Eur J Cardiovasc Prev Rehabil* 2007; 14:547-54.
6. Shibeshi WA, Young-Xu Y, Blatt CM. Anxiety worsens prognosis in patients with coronary artery disease. *J Am Coll Cardiol* 2007; 49:2021-7.
7. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol* 2003; 42:1801-7.
8. Grace SL, Abbey SE, Irvine J, Shnek ZM, Stewart DE. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. *Psychother Psychosom* 2004; 73:344-52.

9. Kubzansky LD, Kawachi I. Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. *Ann Behav Med* 1998; 20:47-58.
10. Haines AP, Imeson JD, Meade TW. Phobic anxiety and ischaemic heart disease. *Br Med J* 1987; 295:297-9.
11. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation* 1994; 89:1992-7.
12. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study. *Circulation* 1994; 90:2225-9.
13. Kubzansky LD, Kawachi I, Spiro A 3rd, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation* 1997; 95:818-24.
14. Shen BJ, Avivi YE, Todaro JF, et al. Anxiety characteristics independently and prospectively predict myocardial infarction in men. *J Am Coll Cardiol* 2008; 51:113-9.
15. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: The HUNT study. *Psychosom Med* 2007; 69:323-31.
16. Yasuda N, Mino Y, Koda S, Ohara H. The differential influence of distinct clusters of psychiatric symptoms, as assessed by the General Health Questionnaire, on cause of death in older persons living in a rural community of Japan. *J Am Geriatr Soc* 2002; 50:313-20.
17. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283:2008 –12.

18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Ann Intern Med* 2009; 151:W65-94.
19. Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, Hjerkin EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovasc Disord* 2009; 9:14.
20. Smoller JW, Pollack MH, Wassertheil-Smoller S, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. *Arch Gen Psychiatry* 2007; 64:1153-60.
21. Philips AC, Batty GD, Gale CR et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. *Psychosom Med* 2009; 71:395-403.
22. Ringbäck Weitoft G, Rosén M. Is perceived nervousness and anxiety a predictor of premature mortality and severe morbidity? A longitudinal follow up of the Swedish survey of living conditions. *J Epidemiol Community Health* 2005; 59:794-8.
23. Kubzansky LD, Cole SR, Kawachi I, Vokonas P, Sparrow D. Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study. *Ann Behav Med* 2006; 31:21-9.
24. Haines A, Cooper J, Meade TW. Psychological characteristics and fatal ischaemic heart disease. *Heart* 2001; 85:385-9.
25. Pettiti DB. Of babies and bathwater. *Am J Epidemiol* 1994; 140:779-82.
26. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation* 2005; 111:480-7.

27. Nicholson A, Fuhrer R, Marmot M. Psychological distress as a predictor of CHD events in men: the effect of persistence and components of risk. *Psychosom Med* 2005; 67:522-30.
28. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: the Framingham Offspring Study. *Psychosom Med* 2005; 67:692-6.
29. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *Am J Epidemiol* 1992; 135:854-64.
30. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *BMJ* 1992; 304:1491-4.
31. Thurston RC, Kubzansky LD, Kawachi I, Berkman LF. Do depression and anxiety mediate the link between educational attainment and CHD? *Psychosom Med* 2006; 68:25-32.
32. Vogt T, Pope C, Mullooly J, Hollis J. Mental health status as a predictor of morbidity and mortality: A 15-year follow-up of members of a health maintenance organization. *Am J Public Health* 1994; 84:227-31.
33. Gafarov VV, Gromova HA, Gagulin IV, Ekimova YC, Santrapinskiy DK. Arterial hypertension, myocardial infarction and stroke: risk of development and psychosocial factors. *Alaska Med* 2007; 49:117-9.
34. Denollet J, Maas K, Knottnerus A, Keyzer JJ, Pop VJ. Anxiety predicted premature all-cause and cardiovascular death in a 10-year follow-up of middle-aged women. *J Clin Epidemiol* 2009; 62:452-6.

35. Rosengren A, Tibblin G, Wilhelmsen L. Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. *Am J Cardiol* 1991; 68:1171-5.
36. Jakobsen AH, Foldager L, Parker G, Munk-Jørgensen P. Quantifying links between acute myocardial infarction and depression, anxiety and schizophrenia using case register databases. *J Affect Disord* 2008; 109:177-81.
37. Gomez-Caminero A, Blumenthal WA, Russo LJ, Brown RR, Castilla-Puentes R. Does panic disorder increase the risk of coronary heart disease? A cohort study of a national managed care database. *Psychosom Med* 2005; 67:688-91.
38. Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. *Eur Heart J* 2008; 29:2981-8.
39. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry* 2007; 22:613-26.
40. Kubzansky LD, Koenen KC, Jones C, Eaton WW. A prospective study of posttraumatic stress disorder symptoms and coronary heart disease in women. *Health Psychol* 2009; 28:125-30.
41. Boyle SH, Michalek JE, Suarez EC. Covariation of psychological attributes and incident coronary heart disease in U.S. Air Force veterans of the Vietnam war. *Psychosom Med* 2006; 68:844-50.
42. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychol Bull* 2005; 131:260-300.

43. Denollet J. Depression, anxiety and trait negative affect as predictors of cardiac events: ten years after. *Psychosom Med* 2008; 70:949-51.
44. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease. *J Am Coll Cardiol* 2009; 53:936-46.
45. Paterniti S, Zureik M, Ducimetière P, Touboul PJ, Fève JM, Alperovitch A. Sustained anxiety and 4-year progression of carotid atherosclerosis. *Arterioscler Thromb Vasc Biol* 2001; 21:136-41.
46. Martens EJ, Nyklíček I, Szsabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. *Psychol Med* 2008; 38:375-83.
47. van den Broek KC, Nyklíček I, van der Voort PH, Alings M, Meijer A, Denollet J. Risk of ventricular arrhythmia after implantable defibrillator treatment in anxious Type D patients. *J Am Coll Cardiol* 2009; 54:531-7.
48. Watkins LL, Blumenthal JA, Davidson JR, Babyak MA, McCants CB Jr, Sketh MH Jr. Phobic anxiety, depression, and risk of ventricular arrhythmias in patients with coronary heart disease. *Psychosom Med* 2006; 68:651-6.
49. Bonnet F, Irving K, Terra JL, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis* 2005; 178:339-44.
50. Davidson JR. First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry* 2009; 70:25-31.
51. Janeway D. An integrated approach to the diagnosis and treatment of anxiety within the practice of cardiology. *Cardiol Rev* 2009; 17:36-43.

52. Kubzansky LD, Koenen KC, Spiro A 3rd, Vokonas PS, Sparrow D. Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. *Arch Gen Psychiatry* 2007; 64:109-16.

Figure legends

Figure 1

Flow-chart of literature search

* Both reports of Haines et al. [10,24] were included; one with cardiac death [24] and one with non-fatal MI [10] as endpoint. CHD= coronary heart disease; MI= myocardial infarction.

Figure 2

Anxiety and risk of incident coronary heart disease

Figure 3

Funnel plot of selected studies with possible missing studies imputed

Figure 1

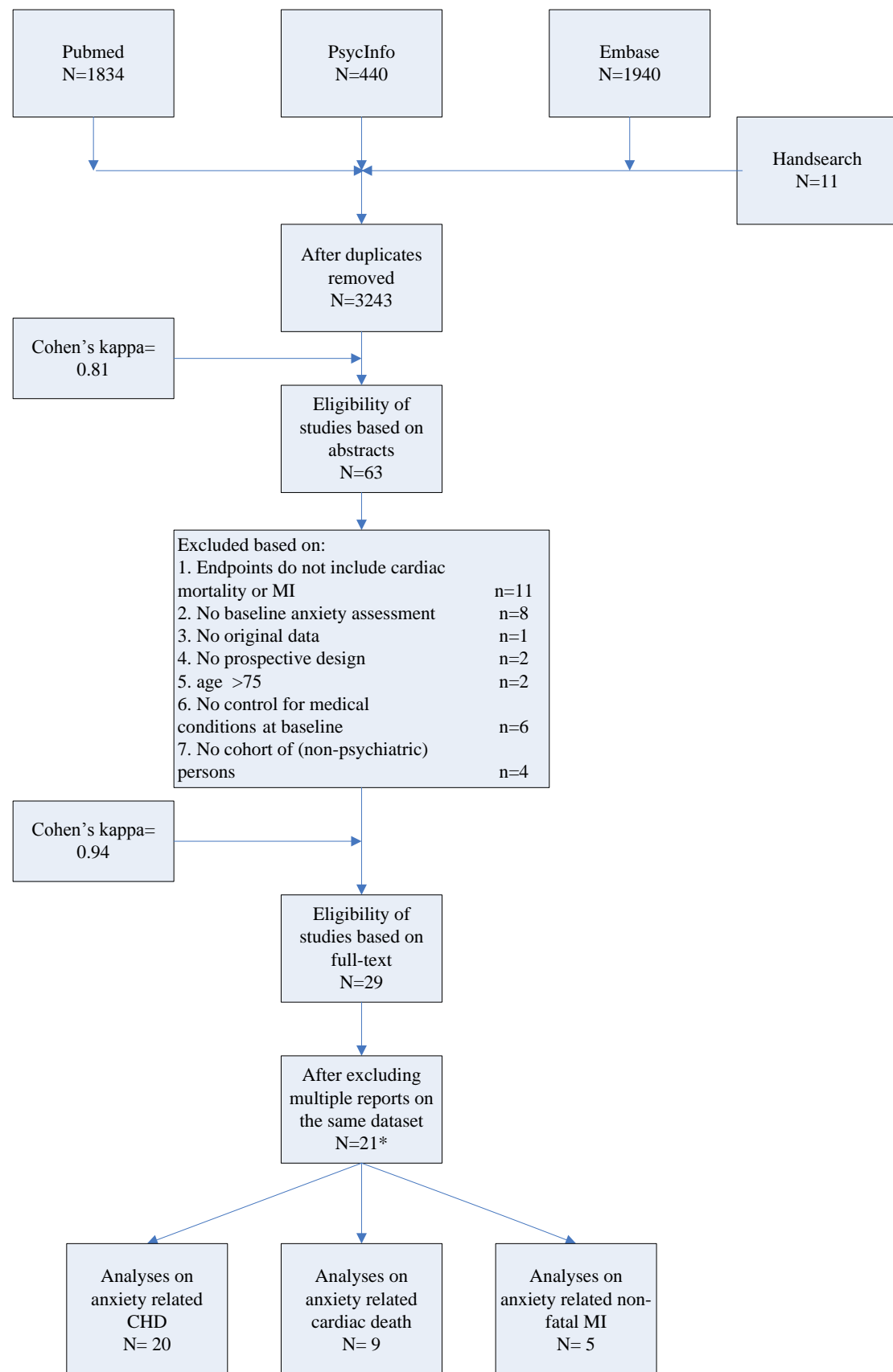


Figure 2

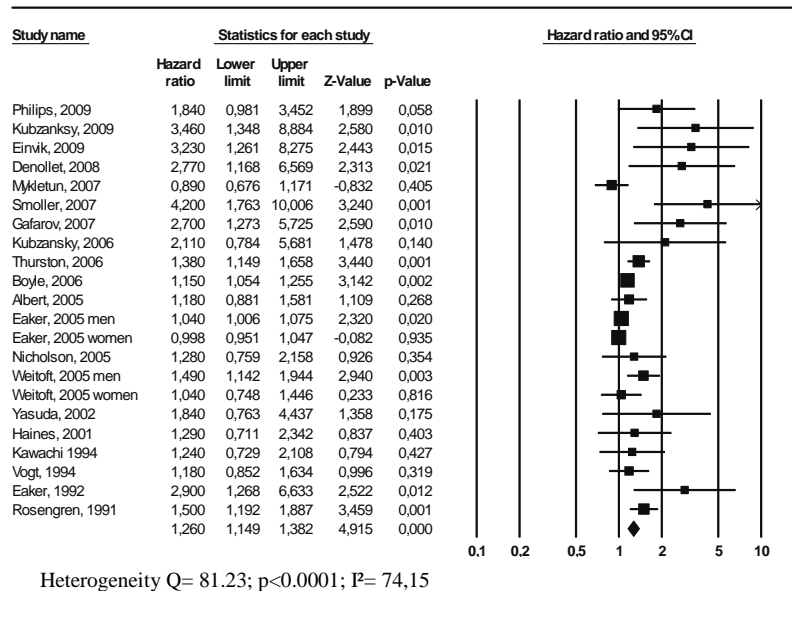


Figure 3

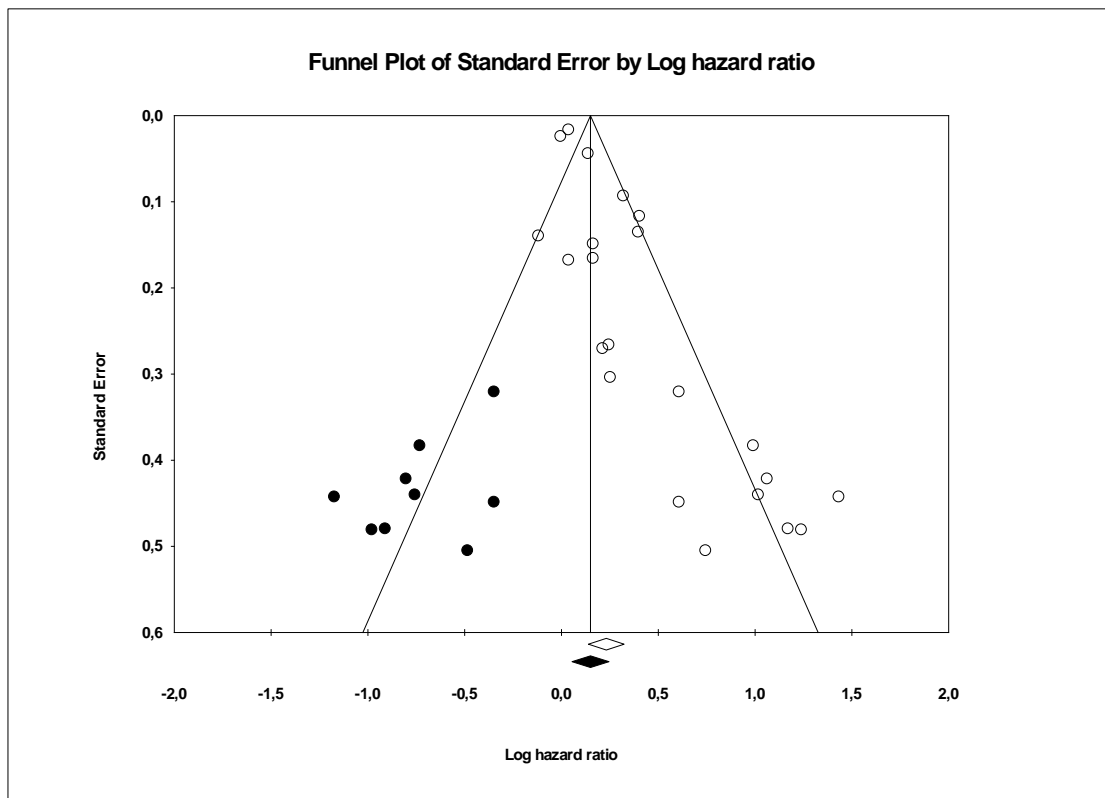


Table 1 Overview of selected studies investigating the association of anxiety with incident CHD

Study	n	Mean age (yr)	Male (%)	Nation and year of Baseline assessment	Participation (%)	Lost to FU (%)	Instrument	Anxiety type	FU (yr)	Endpoints
Phillips, 2009 (21)	4256	38	100	USA, 1986	69	0	DIS	Generalized anxiety disorder	14.6	Cardiac mortality
Kubzansky, 2009 (38)	1059	44	0	USA, 1982	NA	23.6	NIMH DIS	PTSD symptoms	14.0	Cardiac events *
Einvik, 2009 (19)	433	NA	100	Norway, 1997	72	0	HADS-A	General	3.0	Cardiovascular events †
Denollet, 2008 (34)	5073	50	0	The Netherlands, 1994	83	0	EDS Anxiety subscale	General	10.0	Cardiac mortality
Mykletun, 2007 (15)	61349	48	NA	Norway, 1995	66	NA	HADS-A	General	4.4	Cardiac mortality
Smoller, 2007 (20)	3369	66	0	USA, 1997	NA	0.03	Questionnaire based on DSM-IV	Panic attacks	5.3	Cardiac events ‡
Gafarov, 2007 (33)	2149	NA	100	Russia, 1984	NA	NA	STAI	General	20.0	MI

Kubzansky, 2006 (23)	1306	61	100	USA, 1986	82.4	NA	MMPI-2 Anxiety subscale	General	10.9	Non-fatal MI and cardiac mortality
Thurston, 2006 (31)	6265	NA	46	USA, 1971	70	0	GWB-A	General	15.1	Cardiac events §
Boyle, 2006 (39)	2105	47	100	USA, 1985	NA	3.0	MMPI-2	General	15.0	IHD
Albert, 2005 (26)	72359	54	0	USA, 1988	NA	2.0	CCI Phobia index	Phobic	12.0	Non-fatal MI and cardiac mortality
Eaker, 2005 (28)	3682	49	48	USA, 1984	NA	<5	Tension and Symptoms of Anxiety Scales	General	10.0	Cardiac events
Nicholson, 2005 (27)	5449	NA	100	UK, 1985	74	NA	GHQ-30 Anxiety subscale	General	6.8	Cardiac events ‡
Ringbäck Weitoft, 2005 (22)	34511	43	50	Sweden, 1980	79-86	NA	Single question	General	5.0	IHD
Yasuda, 2002 (16)	817	72	39	Japan, 1991	92	2.8	GHQ-30 Anxiety subscale	General	7.5	Cardiac mortality
Haines, 2001 (24)	1408	NA	100	UK, 1972	80	NA	CCI Phobia index	Phobic	20.9	Cardiac mortality

Kawachi, 1994 (11)	33999	NA	100	USA, 1986	NA	4.0	CCI Phobia index	Phobic	2.0	Non-fatal MI and cardiac mortality
Vogt, 1994 (32)	2573	NA	46	USA, 1970	92	0	Bradburn Worries Index	Worry	15.0	IHD
Eaker, 1992 (29)	749	NA	0	USA, 1965	NA	NA	Tension and Symptoms of Anxiety Scales	General	20.0	Cardiac events †
Rosengren, 1991 (35)	6935	NA	100	Sweden, 1970	76	NA	Single question	General	11.8	Cardiac events †
Haines, 1987 (10)	1342	NA	100	UK, 1972	80	2.8	CCI Phobia index	Phobic	6.7	Non-fatal MI

CCI= Crown-Crisp Index; DIS= Diagnostic Interview Schedule; DSM= Diagnostic Statistical Manual; EDS= Edinburgh Depression Scale; GHQ= General Health Questionnaire; GWB-A= General Well-Being Schedule anxiety subscale; HADS-A= Hospital Anxiety and Depression Scale, anxiety subscale; IHD= ischemic heart disease; MI= myocardial infarction; MMPI= Minnesota Multiphasic Personality Inventory; NA= not available; PTSD= Post traumatic stress disorder; STAI= Stait Trait Anxiety Index.

*
= angina pectoris, non-fatal MI, fatal MI and other cardiac death

† = cardiac death, non-fatal MI, percutaneous coronary intervention, CABG, cerebral stroke, surgery on abdominal aortic aneurysm and revascularization in peripheral arterial disease

‡ = non-fatal MI and cardiac death

§ = MI, other acute and subacute ischemic heart disease, other forms of chronic ischemic heart disease

|| = non-fatal MI, coronary insufficiency and cardiac death

Table 2 Overview of bivariate and multivariable associations of anxiety with incident CHD

<i>Study</i>	<i>Adjustment</i>	<i>HR/RR/OR</i> <i>(95%CI)</i>	<i>Adjustment</i>	HR/RR/OR (95%CI)
Phillips, 2009 (21)	Age	2.89 (1.59-5.23)	Age, place of service, ethnicity, marital status, smoking habit, alcohol consumption, IQ at enlistment, household income in midlife, BMI, total cholesterol, SBP, blood glucose, and somatic illness.	1.84 (0.98-3.45)
Kubzanksy, 2009 (38)	Age	3.21 (1.29-7.98)	Age, race/ethnicity, smoking status, history of high blood pressure, history of diabetes, alcohol use, education, income.	3.46 (1.35-8.90)
Einvik, 2009 (19)	-	3.17 (1.28-7.82)	Age, previous cardiovascular disease, current smoking, level of serum glucose, diabetes, SBP, LDL-cholesterol, alcohol use, BMI, treatment modality.	3.23 (1.26-8.27) *
Denollet, 2008 (34)	Age	2.74 (1.15-6.49)	Age, education, living alone, hormone intake, smoking, alcohol, physical activity, BMI, hypertension, diabetes, depressive symptoms.	2.77 (1.17-6.58)
Mykletun, 2007 (15)	Age and gender	1.10 (0.84-1.43)	Age, gender, somatic symptoms/diagnoses, physical impairment, health-related behavior (smoking, alcohol problems, physical activity) educational level and SES, physical measurement (BMI, DBP, total cholesterol level).	0.89 (0.67-1.16)
Smoller, 2007 (20)	Age, race, income	1.92 (1.20-3.07)	Age, race, income, BMI, alcohol, hormone use, high cholesterol level requiring medication, history of diabetes mellitus treatment, smoking, depression, history of atrial fibrillation, hypertension status, moderate to strenuous activity for longer than 20 minutes 3 or more times a week, and history of MI, CABG, PTCA, or stroke.	4.20 (1.76-9.99)
Gafarov, 2007 (33)	-	2.70 (1.27-5.71)	“	“

Kubzansky, 2006 (23)	Age	2.11 (0.8-5.6)	Age, BMI, smoking status, SBP and DBP, serum cholesterol, family history of CHD, alcohol use, education.	2.11 (0.8-5.8)
Thurston, 2006 (31)	Age and gender	1.56 (1.31-1.86)	Age, gender, marital status, race/ethnicity, smoking status, aerobic exercise, alcohol use, SBP, DBP, BMI, cholesterol, hypertension, diabetes status.	1.38 (1.15-1.66)
Boyle, 2006 (39)	Age	1.18 (1.08-1.29)	Age, total cholesterol, smoking status, hypertensive status, diabetes status, high density lipoprotein and BMI.	1.15 (1.05-1.25)
Albert, 2005 (26)	Age	1.55 (1.16-2.08)	Age, smoking status, BMI, alcohol intake, menopausal status and hormone use, parental history of MI, physical activity, aspirin use, valium use, history of hypertension, hypercholesterolemia and diabetes.	1.18 (0.88-1.58)
Eaker, 2005 (28) men	-	NA	Age, SBP, BMI, current cigarette smoking, diabetes, and total cholesterol/high-density cholesterol.	1.04 (1.01-1.08) †
Eaker, 2005 (28) women	-	NA	Age, SBP, BMI, current cigarette smoking, diabetes, and total cholesterol/high-density cholesterol.	1.00 (0.95-1.05) †
Nicholson, 2005 (27)	Age	1.28 (0.76-2.16)	“	“
Ringbäck Weitoft, 2005 (22) men	Age	1,82 (1.35-2.45)	Age, smoking, longstanding illness, education.	1,49 (1,14-1,94)
Ringbäck Weitoft, 2005 (22) women	Age	1.28 (0.94-1.74)	Age, smoking, longstanding illness, education.	1.04 (0.75-1.45)
Yasuda, 2002 (16)	-	NA	Age, gender, chronic conditions under treatment, regular physical activity, and availability of close or casual neighbors.	1.84 (0.76-4.42)
Haines, 2001 (24)	-	NA	Age, smoking, BMI, fibrinogen, factor VII, SBP, cholesterol, social class.	1.29 (0.71-2.34)

Kawachi, 1994 (11)	Age	1.40 (0.83-2.37)	Age, smoking, alcohol, BMI, history of hypertension, diabetes mellitus, hypercholesterolemia, parental history of MI before the age of 60 years, physical activity.	1.24 (0.73-2.11)
Vogt, 1994 (32)	-	2.34 (1.72-3.20)	Age, gender, self-reported health status, self-reported social class, cigarette smoking status, duration of health plan membership.	1.18 (0.85-1.63)
Eaker, 1992 (29)	NA	NA	Age, SBP, ratio of the serum total cholesterol to high-density lipoprotein cholesterol, diabetes, cigarette smoking and BMI.	2.9 (1.3-6.8)
Rosengren, 1991 (35)	-	1.6 (1.3-2.0)	Age, SBP, serum cholesterol, smoking, BMI, diabetes, family history of MI, occupational class, marital state, leisure time physical activity, registration for alcohol abuse.	1.5 (1.2-1.9)
Haines, 1987 (10)	-	NA	Age, smoking habit, social class, shift (night or day), SBP, fibrinogen, cholesterol, factor VII activity.	1.26 (0.62-2.54)

BMI= body mass index; CABG= coronary artery bypass graft; CHD= coronary heart disease; DBP= diastolic blood pressure; MI= myocardial infarction; NA= not available; PTCA= percutaneous transluminal coronary angioplasty; SBP= systolic blood pressure; SES= socioeconomic status.

Bolded numbers are statistically significant

* = HR received from author

† = based on own calculations